# Cetuximab as Second-Line Therapy in Patients with Metastatic Esophageal Adenocarcinoma

## *A Phase II Southwest Oncology Group Study (S0415)*

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**Introduction:** Esophageal adenocarcinomas commonly express the epidermal growth factor receptor. This trial assessed the 6-month overall survival probability in metastatic esophageal cancer patients treated with cetuximab as second-line therapy.

**Methods:** This was a multicenter, open-label phase II study of single-agent cetuximab for metastatic esophageal adenocarcinoma patients who failed one prior chemotherapy regimen. Adequate organ function and Zubrod performance status of 0 to 2 were required. Patients received cetuximab 400 mg/m$^2$ intravenously (IV) on week 1 and 250 mg/m$^2$ IV weekly thereafter. The primary objective was to determine 6-month overall survival. Secondary end points included progression-free survival, response rate, and toxicity. Tumor tissue was collected for correlative studies.

**Results:** Sixty-three patients were registered, with eight ineligible or never treated. Fifty-five eligible patients (49 men, 6 women; median age = 61.2 years [range, 30.7–88.5]) were enrolled. Twenty patients survived more than 6 months for a 6-month overall survival rate of 36% (95% confidence interval [CI]: 24–50%). The median overall survival was 4.0 months (95% CI: 3.2–5.9). Median progression-free survival was 1.8 months (95% CI: 1.7–1.9). One partial response and two unconfirmed partial responses were observed. Two patients experienced grade 4 fatigue. There was one treatment-related death due to pneumonitis. Germline polymorphisms of epidermal growth factor receptor, epidermal growth factor, interleukin (IL)-8, cyclooxygenase (COX)-2, vascular epidermal growth factor receptor (VEGF), CCND1, neuropilin 1 (NRP1), and *K-ras* mutational status were not associated with response or survival.

**Conclusions:** The 6-month overall survival rate of 36% observed on this study failed to meet the primary survival objective. Thus, cetuximab alone cannot be recommended in the second-line treatment of metastatic esophageal cancer.

**Key Words:** Cetuximab, Esophageal cancer, Second-line therapy.

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It is estimated that in 2009, 16,470 patients will be diagnosed with esophageal cancer, and that 14,530 will die of the disease.[1] Because a significant proportion of these patients present with or will develop metastatic disease, the prognosis is poor. Chemotherapy has had only a minimal impact on the natural history of metastatic esophageal cancer. First-line chemotherapy results in median survival of up to 11.2 months.[2] Little data exist on the benefit of second-line therapy, with one study demonstrating a median time to progression of 7 weeks and a median survival of 5 months[3] and another with a median survival of 5.6 months in 423 patients.[4] A recent second-line randomized study of irinotecan versus best supportive care in patients with metastatic gastric and gastroesophageal adenocarcinomas showed an improvement in overall survival for the irinotecan arm (123 versus 72.5 days).[5] To improve the outcome of patients with metastatic esophageal cancer, it is imperative that more effective agents be developed.

The epidermal growth factor receptor (EGFR) is a commonly expressed transmembrane glycoprotein of the tyrosine kinase growth factor receptor family. EGFR is expressed in many normal human tissues, and activation of this proto-oncogene results in overexpression in many types of human tumors cells in culture.[6] To inhibit proliferation of EGFR-rich cells, EGFR antagonists, which block the ligand-binding site, have been developed. Specifically, monoclonal antibodies to EGFR have been shown to inhibit the proliferation of cells that produce both transforming growth factor and epidermal growth factor (EGF).[7] Approximately 65% of esophageal adenocarcinomas have been shown to overexpress EGFR, and amplification of the EGFR gene has been found in approximately 11%. Patients with esophageal

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adenocarcinomas overexpressing EGFR seem to have a poorer prognosis than those whose tumors do not overexpress EGFR.[8]

Cetuximab, a chimerized antibody of the IgG1 subclass, was originally derived from a mouse myeloma cell line.[9] Cetuximab blocks binding of EGF and transforming growth factor-$\alpha$ to EGFR and inhibits ligand-induced activation of this tyrosine kinase receptor. Cetuximab also stimulates EGFR internalization, effectively removing the receptor from the cell surface for interaction with ligand.[10] Studies in advanced colorectal cancer have shown cetuximab to have clinical antitumor activity, with an 11% response rate in monotherapy and a 23% response rate in combination with irinotecan.[11] Cetuximab has also been approved for use in head and neck cancer with radiotherapy for locally advanced disease or with platinum-based chemotherapy for recurrent or metastatic disease.

In a phase I multiple-dose clinical trial conducted to examine the tolerability of anti-EGFR in patients with advanced cancer, one of three esophageal cancer patients demonstrated stable disease for 7 months.[12]

Given the poor prognosis of patients with advanced esophageal cancer, the preclinical rationale for EGFR antagonists, and the early clinical data, this phase II study examined cetuximab in metastatic esophageal cancer patients who had failed first-line chemotherapy.

## PATIENTS AND METHODS

### Patients

Eligibility included the following criteria. (1) A histologic diagnosis of adenocarcinoma of the thoracic esophagus or gastroesophageal junction. (2) Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST). (3) One prior regimen of chemotherapy for metastatic or recurrent disease. Patients may have received one prior regimen of adjuvant or neoadjuvant chemotherapy if administered at the time of initial diagnosis with localized disease. (4) No prior cetuximab or other therapy targeting the EGF pathway. (5) Patients were required to have a Zubrod performance status of 0, 1, or 2 and adequate bone marrow, hepatic, and renal function. Prior radiation and thoracoabdominal surgery were allowed.

All patients or their guardians provided written informed consent in accordance with institutional and federal guidelines that included permission for the submission of tissue for correlative science. This study (ClinicalTrials.govIdentifier: NCT00096031) was approved by a local Human Investigation Committees and was conducted in accord with an assurance filed with and approved by the Cancer Therapy and Evaluation Program Central Institutional Review Board, National Cancer Institute, Department of Health and Human Services.

### Study Design

This phase II, open-label, multicenter trial was administered and monitored by Southwest Oncology Group. Patients received a loading dose of cetuximab at 400 mg/m$^2$ intravenously (IV) over 2 hours on day 1 and on subsequent weeks cetuximab at 250 mg /m$^2$ IV over 1 hour. Patients were premedicated with diphenhydramine 50 mg IV or PO 30 to 60 minutes before cetuximab. Treatment continued until disease progression or unacceptable toxicity.

Baseline assessments included medical history and physical examination, performance status, complete blood count with differential and platelet count, serum chemistries, diagnostic tumor imaging, and tumor markers as clinically indicated. During the study, complete blood count with differential and platelet count was performed weekly, history and physical examination were performed every other week, and serum chemistries were performed at the start of every 4-week cycle.

Patients were monitored for toxicity weekly, with adverse events reported to the Southwest Oncology Group Statistical Center after every 28-day treatment cycle. Toxicity was graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events version 3 criteria. In addition, serious adverse events were reported to the NCI through the AdEERS reporting system. Tumor response using RECIST criteria was assessed every 8 weeks.

### Correlative Science

#### Genotyping

Formalin-fixed paraffin-embedded tumor samples were submitted and examined for *K-ras* mutational status and polymorphisms for EGFR, EGF, IL-8, VEGF, COX-2, NRP1, and CCND1. Genomic DNA was extracted using the QIAamp kit (Qiagen, Valencia, CA). Genotype analysis was performed for most polymorphisms using polymerase chain reaction-restriction fragment length polymorphism technique.

Forward and reverse primers were used for polymerase chain reaction (PCR) amplification, and PCR products were digested by restriction enzymes (New England Biolab, Ipswich, MA). Digested fragments were separated on a 4% NuSieve ethidium bromide-stained agarose gel. In case no matching restriction enzyme was found, direct sequencing was used.

#### *K-ras* Mutational Analysis

Genomic DNA from microdissected tumor samples was extracted, and forward and reverse primers for exon 2, codon 12, and 13 *K-ras* mutation were used for PCR amplification. PCR fragments were sequenced on an ABI 3100A Capillary Genetic Analyzer (Applied Biosystems, Foster City, CA) and analyzed in antisense direction for the presence of heterozygous mutations. DNA sequence analyses were performed by using the ABI Sequencing Scanner v1.0 (Applied Biosystems).

### Statistical Design

This study was monitored by the Data and Safety Monitoring Committee of the Southwest Oncology Group. The primary end point of this trial was overall survival. Based on historical survival rates in this population, it was judged that this therapy would be of considerable interest if the overall 6-month survival probability was 50% or greater but

 

would be of no further interest if it was 30% or less. Secondary objectives included (1) assessment of overall response rate, (2) progression-free survival and time to treatment failure, (3) evaluation of toxicity in these patients, and (4) exploratory analyses of germline polymorphisms of genes involved in the EGFR, DNA repair, and angiogenesis pathways.

A two-stage design was used for patient accrual. Thirty patients were to be accrued to the first stage. If at least nine of these survived past 6 months, an additional 25 would be accrued. Of these 55 patients, if a 6-month survival rate of at least 42% was observed, the null hypothesis would be rejected, and this regimen would be considered for further study. This design has a power of 90% at a significance level of 0.04. Overall survival curve was plotted using the Kaplan-Meier method.[13]

**TABLE 1.** Baseline Patient Characteristics

| | |
|---|---|
| Median age (range) | 61 (31–89) |
| Gender | |
| Male | 49 (89%) |
| Female | 6 (11%) |
| Performance status | |
| 0 | 14 (25%) |
| 1 | 36 (65%) |
| 2 | 5 (10%) |
| Disease status | |
| Initial diagnosis | 16 (29%) |
| Recurrence | 39 (71%) |
| Prior surgery | 20 (36%) |
| Prior radiation | 34 (62%) |
| Number of metastatic sites | |
| 1 | 19 (35%) |
| 2 | 20 (36%) |
| 3+ | 16 (29%) |

## RESULTS

### Patients

The first patient cohort was accrued from February to November 2005, and the study was temporarily closed to assess survival in these patients. The observed survival rate was sufficiently high to reopen the study, and the second cohort of patients was enrolled from April 2006 to January 2007. In total, 63 patients were registered to this study. Eight of these patients are excluded from the analysis. Six of these patients were ineligible: two had a gastric primary; three did not have metastatic disease; and another patient had insufficient baseline documentation. Two additional eligible patients did not receive any treatment and are not evaluable for any end point. The demographic information and patient characteristics for the 55 eligible and evaluable patients are listed in Table 1.

### Treatment Efficacy

The median number of cetuximab doses was 7 (range, 1–40). A major treatment deviation was recorded for one patient who received nonprotocol irinotecan and cisplatin while on study. Of 55 eligible and evaluable patients, 20 survived at least 6 months for a 6-month overall survival rate of 36% (95% confidence interval [CI]: 24–50%). The Kaplan-Meier estimate of median overall survival is 4.0 months (95% CI: 3.2–5.9) (Figure 1). Both median progression-free survival and time to treatment failure are 1.8 months (95% CI: 1.7–1.9).

The objective responses to cetuximab are summarized in Table 2. There were two partial responses and one unconfirmed partial response for an overall response rate of 5% (95% CI: 1–15%). For the nine patients with either a partial response or stable disease, the median overall survival is 8.3 months (range, 4.1–11.3), and the median progression-free survival is 4.0 months (range, 3.0–11.3).

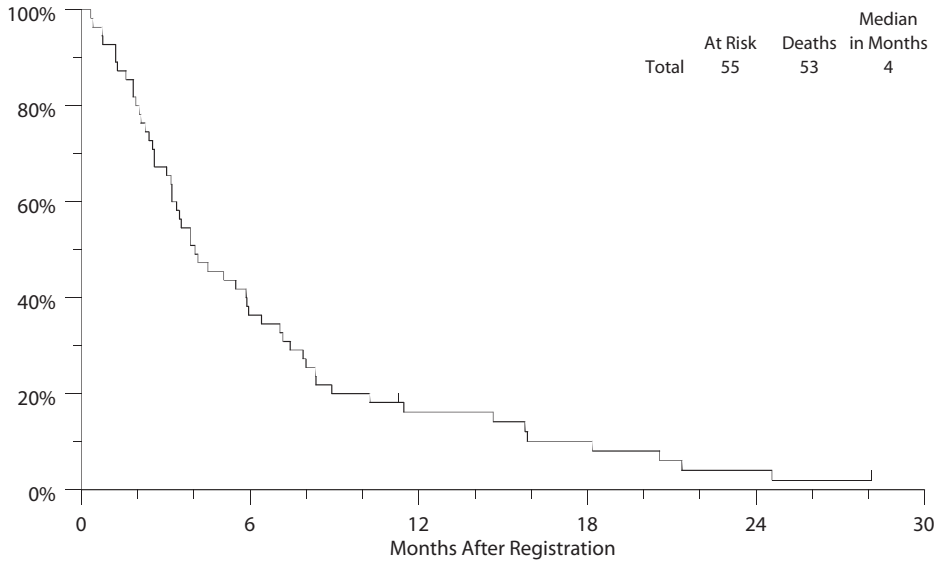


**FIGURE 1.** The Kaplan-Meier curve for overall survival in patients with metastatic esophageal cancer treated with cetuximab as second-line therapy.

**TABLE 2.** Treatment-Related Adverse Events

| Adverse Event | Grade 2, *n* (%) | Grade 3+, *n* (%) |
|---|---|---|
| Dermatologic | 20 (36) | 4 (7) |
| Flu-like symptoms | 13 (24) | 8 (15)[a] |
| Gastrointestinal | 16 (29) | 4 (7) |
| Hematologic | 3 (5) | 1 (2) |
| Immunological | 3 (5) | 1 (2) |
| Infection | 2 (4) | 1 (2) |
| Pulmonary | 2 (4) | 2 (4)[b] |
| Metabolic | 4 (7) | 6 (11) |
| Neurologic | 2 (4) | 1 (2) |
| Pain | 9 (16) | 5 (9) |

[a] Includes two patients with grade 4 fatigue.
[b] Includes one patient with grade 5 pneumonitis.

## Toxicity

The frequency and severity of cetuximab-related toxicities is shown in Table 2. Two patients experienced grade 4 fatigue. Twenty patients experienced grade 3 toxicities, including four patients with grade 3 rash. There was one treatment-related death due to pneumonitis. Dose reductions or treatment delays were reported for 29 of 55 patients (53%).

## Correlative Science

Sufficient tissue was available for analysis in 42 of 55 patients. The germline polymorphisms studied included EGFR, EGF, IL-8, COX-2, VEGF, CCND1, and NRP1.

Polymorphisms, as performed in this trial, were not found to be associated with response, overall survival, progression-free survival, time to treatment failure, or toxicity for any of the genes tested.

*K-ras* mutation was present in 1 of 42 patients (2%). Table 3 summarizes these findings.

**TABLE 3.** Results of Biomarker Analyses

| Marker | *n* (%) | Median OS (95% CI), mo | *p*[a] |
|---|---|---|---|
| CCND1 +870A>G (*n* = 39) (*rs 17852153*) | | | |
| AA | 8 (21%) | 2.1 (1.2–5.9) | 0.18 |
| AG | 23 (58%) | 5.5 (3.4–7.2) | |
| GG | 8 (21%) | 3.7 (1.8–15.9) | |
| EGFR +497 G>A (*n* = 38) (*rs 11543848*) | | | |
| AA/AG | 31 (81%) | 3.9 (3.0–7.1) | 0.27 |
| GG | 7 (19%) | 3.5 (1.8–6.4) | |
| IL-8 −251 T>A (*n* = 39) (*rs 4073*) | | | |
| AA | 8 (21%) | 5.7 (3.5–6.4) | 0.60 |
| AT | 17 (44%) | 3.9 (2.4–8.3) | |
| TT | 14 (35%) | 3.2 (1.3–5.8) | |
| COX-2 +8473 T>C (*n* = 33) (*rs 5275*) | | | |
| CC | 7 (21%) | 3.2 (1.6–8.3) | 0.69 |
| CT | 15 (46%) | 3.9 (2.6–6.4) | |
| TT | 11 (33%) | 4.1 (2.1–8.3) | |
| EGF +61 A>G (*n* = 37) (*rs 4444903*) | | | |
| AA | 10 (27%) | 6.1 (3.2–8.0) | 0.94 |
| AG | 10 (27%) | 3.2 (1.6–8.3) | |
| GG | 17 (46%) | 3.5 (2.6–7.1) | |
| VEGF +936 C>T (*n* = 40) (*rs 3025039*) | | | |
| CC | 34 (85%) | 3.7 (2.6–5.9) | 0.26 |
| CT | 6 (15%) | 7.7 (5.5–11.5) | |
| NRP-1 C>T (*n* = 34) (*rs 3750733*) | | | |
| CC | 10 (29%) | 6.2 (3.9–11.5) | 0.27 |
| CT | 16 (47%) | 3.7 (1.8–5.8) | |
| TT | 8 (24%) | 7.7 (2.4–15.9) | |

[a] *p* values from Cox regression test for heterogeneity across subgroups.
OS, overall survival; CI, confidence interval; COX, cyclooxygenase; EGF, epidermal growth factor; IL, interleukin; VEGF, vascular endothelial growth factor; NRP, Neuropilin.

## DISCUSSION

This phase II trial examined the efficacy and safety of single-agent cetuximab in patients with previously treated metastatic esophageal adenocarcinoma. Patients enrolled on this trial achieved an overall 6-month survival probability of 36%. This represented a failure to meet the primary objective of the study. However, the median survival of 4 months is similar to that reported in the other second-line trials of chemotherapy in metastatic esophageal adenocarcinoma.[3–5] The overall response rate of 5% suggests a similar level of single-agent activity as that seen with cetuximab in patients with refractory metastatic colon cancer.[14] In metastatic colorectal cancer, the addition of cetuximab to cytotoxic chemotherapy increases antitumor response rates.[15,16] Phase II trials in untreated, metastatic gastric, or gastroesophageal junction adenocarcinoma demonstrated that the combination of cetuximab with chemotherapy has a high level of activity, with response rates greater than 40%.[17,18]

Treatment with single-agent cetuximab in this setting was shown to be well tolerated with the frequency of adverse events comparable with that seen in other trials.[14] The frequency and severity of cetuximab-induced rash has been shown to be associated with both response rate and survival.[19] In this study, four patients developed grade 3 rash, three of whom survived for more than 6 months. The patient who died of pneumonitis is concerning because current trials are combining cetuximab with radiation and chemotherapy for esophageal cancer patients. This is in contrast to large studies of cetuximab in both colorectal and head and neck cancers in which no cases of pneumonitis were reported.[20,21] Nonetheless, we recommend that close attention be paid to pulmonary toxicity for patients on these trials.

Evaluation of tissue for a variety of germline polymorphisms failed to show a relationship between genotype and outcome or toxicity for any of the genes tested, although our ability to detect any differences was limited by the lack of objective responses and the small sample size.

Almost all the tumors tested were wild-type *K-ras*, with *K-ras* mutation present in only 1 of 42 patients (2%). Although the three responses in this group of patients were

 

found in patients with wild-type *K-ras* tumors, we see no reason to test patients for *K-ras* mutational status before therapy on current clinical trials for patients with adenocarcinoma of the esophagus. Low frequency of *K-ras* mutations have also been observed in squamous cell carcinoma of the esophagus (0%) and gastric adenocarcinoma (11%).[22,23] This is in contrast to recent data in colorectal cancer, which clearly demonstrates a correlation between *K-ras* status and the efficacy of anti-EGFR targeted therapy.[24,25]

This trial failed to meet the primary end point. Therefore, cetuximab monotherapy is not recommended as second-line therapy in the treatment of metastatic esophageal adenocarcinoma.

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